Βιοϋλικά

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Χειμερινό Εξάμηνο 2015

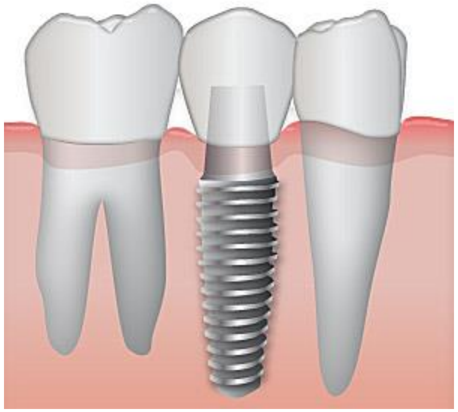
Presentation Outline

- Biomaterials
  - Types
  - Foreign body response
- Porous collagen scaffolds
- The Matrix
- Key Applications of Biomaterials

Biomaterials

Biomaterials

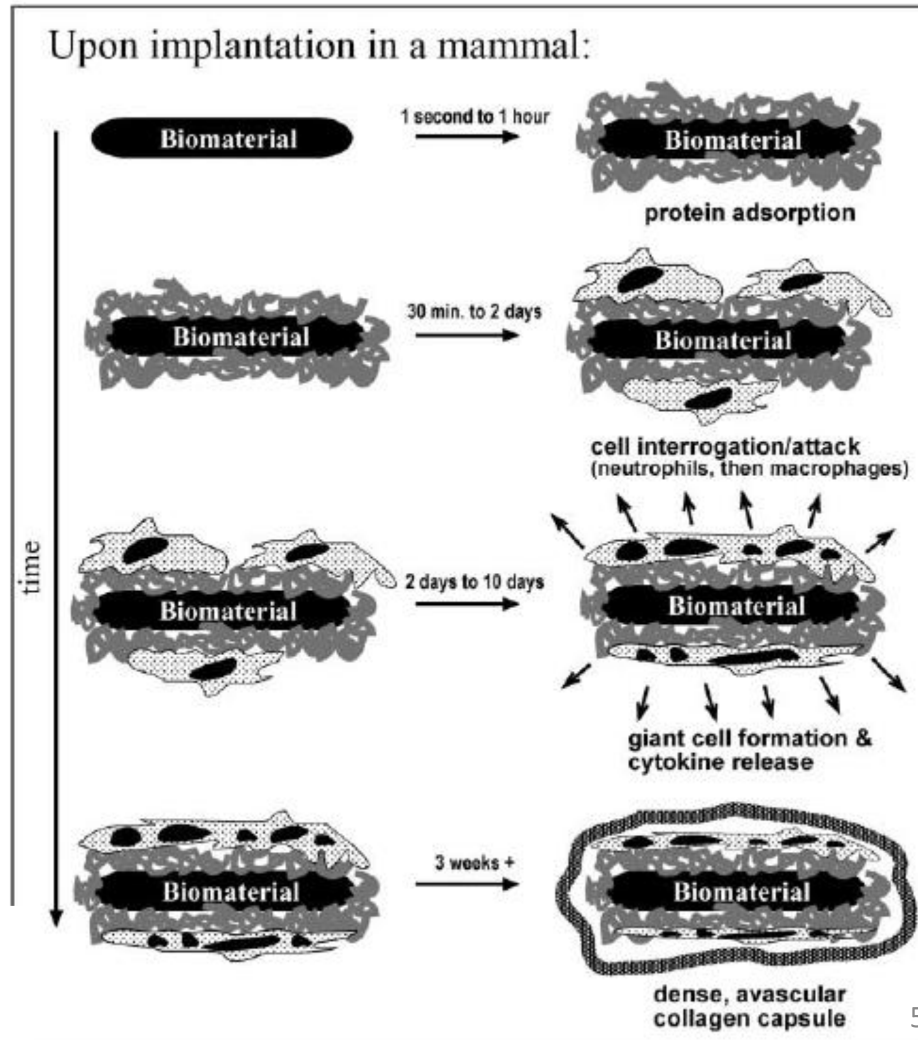
- Materials that interact with cells
  – Not cyto-toxic
  – Could control cell fate



- Two Major Families
  1. Bone Implants
     - Designed to withstand loads
     - Metal, ceramic
  2. Soft biomaterials
     - Utilized in regenerative medicine and *in vitro* cell studies

Foreign Body Response

- Cells try to eliminate objects inside the body not recognized as “self”
- Some biomaterials cause FBR
  - Metal, ceramic implants
- Some don’t cause FBR
  - E.g. collagen scaffolds



Ratner and Bryant, An. Rev. Biomed. Eng., 2004

Types of Biomaterials

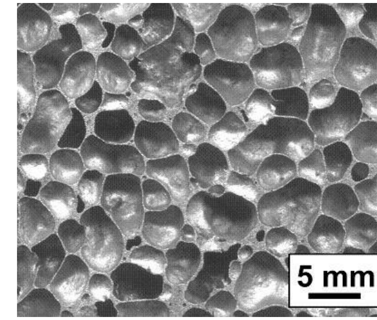
- Sort by structure
  - Scaffolds
  - Gels

- Sort by chemical composition
  - Natural: made of biopolymers (proteins, sugars)
  - Artificial: made of artificial monomers

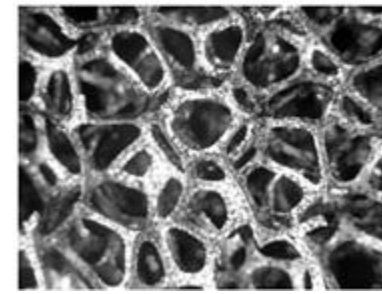
Major Features of Biomaterials

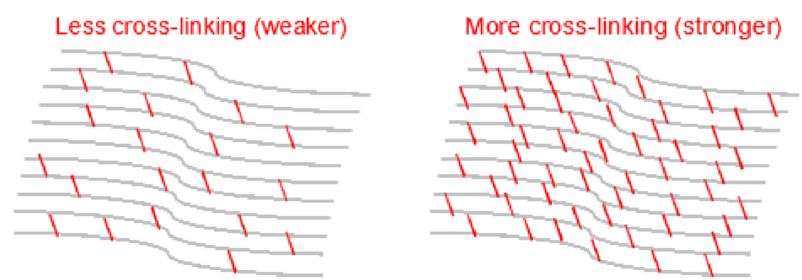
- Chemical Composition
  - Composition
  - Surface chemistry
- Structure
  - Pore size diameter, connectivity, directionality
- Cross-linking
  - Affects *in vivo* degradation rate and mechanical stiffness

Closed foam plastic (foardpanel.com)



Open foam plastic (ultramet.com)

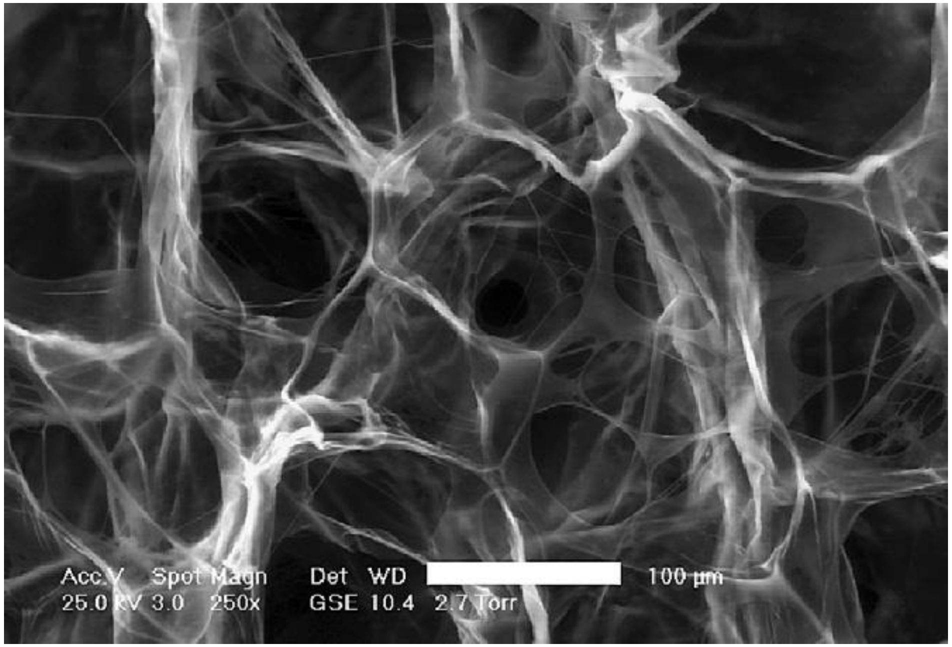




Scaffolds (Ικριώματα)

- Porous biomaterials
  - Sponge-like structure
  - Pore diameter: 10-500 μm
  - Behave like open foam plastics

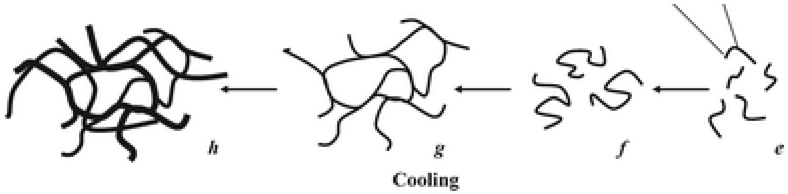
- Fabrication methods
  - Freeze-drying
  - Particle evaporation



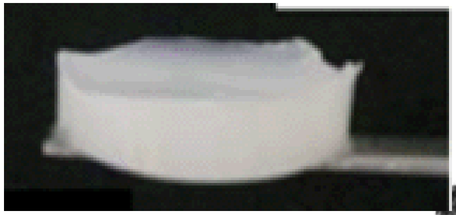
Porous collagen scaffold SEM
(Pek, Biomaterials, 2005)

Gels (Γέλες)

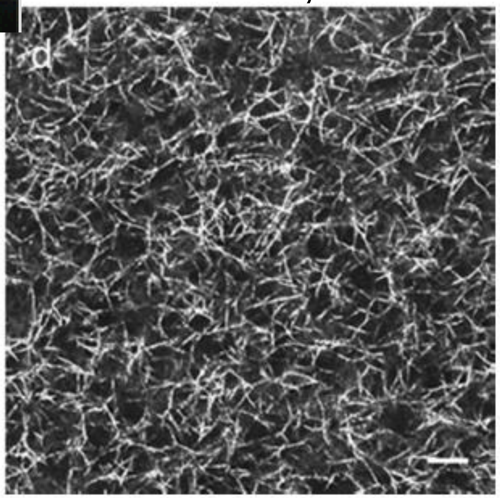
- Fabricated by gelation



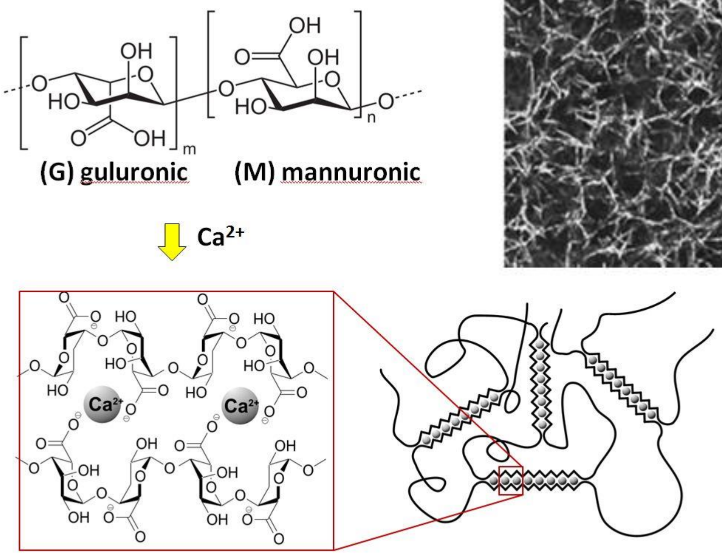
- Outcome
  - Viscous body.. Not solid
  - Pore size ~ 0.5 μm



Moreno-Arotzena, Materials, 2015

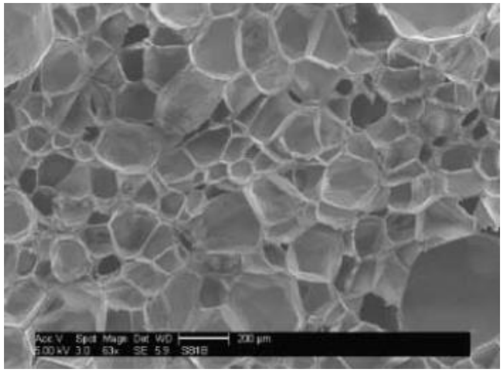


- Examples
  - Fibrin gels
  - Collagen gels
  - Gelatin gels
  - Alginate gels



Functionalized Artificial Biomaterials

- Build from artificial monomers functionalized with key motifs and proteins
  - e.g. RGD functionalization



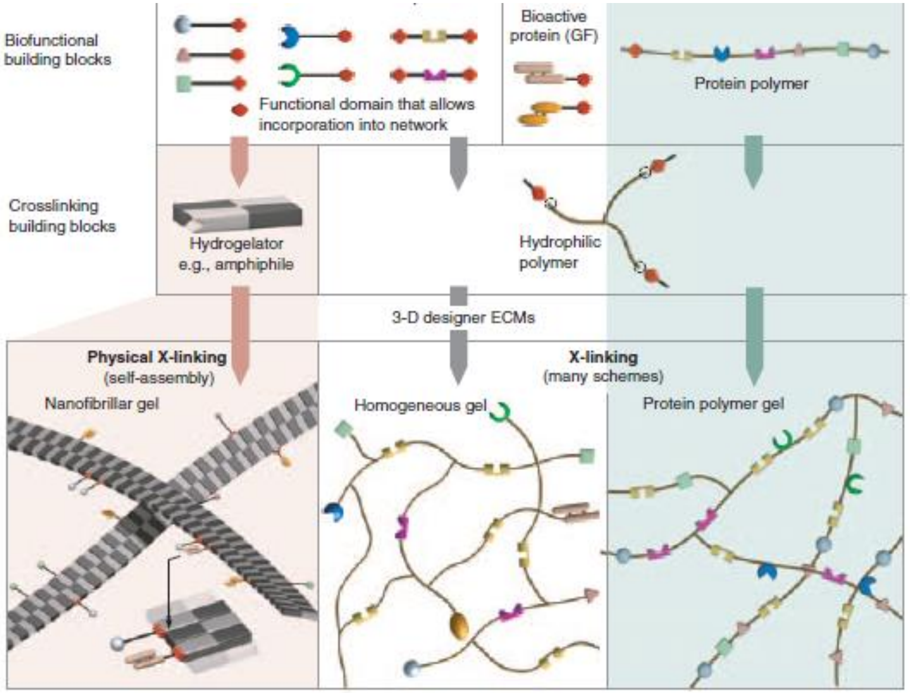
Hydrogel foam (Ratner & Bryant, 2007)

Synthetic biomaterials as instructive extracellular microenvironments for morphogenesis in tissue engineering

M P Lutolf[1,2] & J A Hubbell[1]

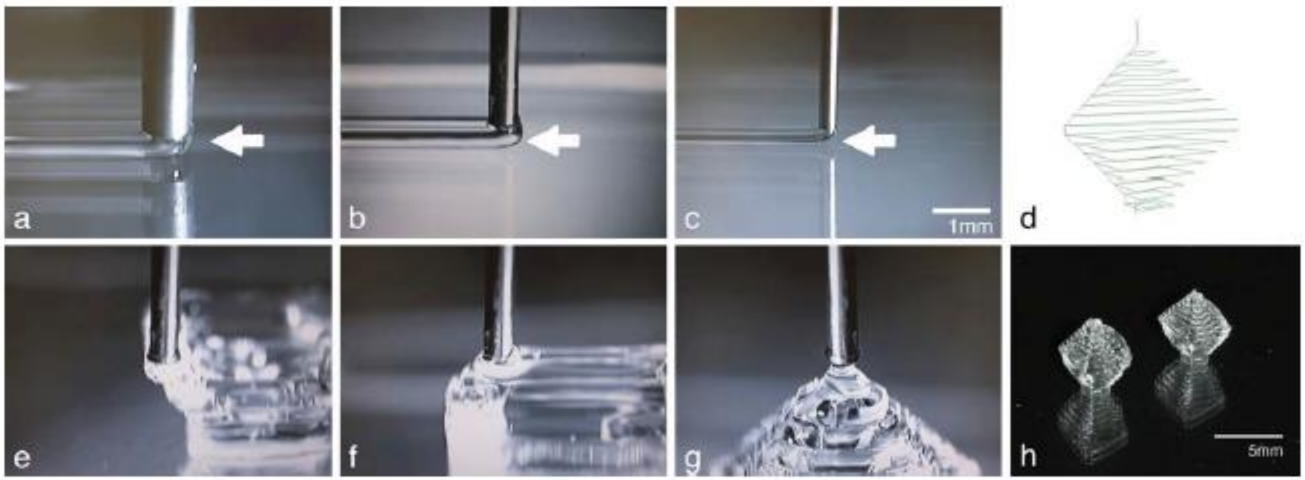
New generations of synthetic biomaterials are being developed at a rapid pace for use as three-dimensional extracellular microenvironments to mimic the regulatory characteristics of natural extracellular matrices (ECMs) and ECM-bound growth factors, both for therapeutic applications and basic biological studies. Recent advances include nanofibrillar networks formed by self-assembly of small building blocks, artificial ECM networks from protein polymers or peptide-conjugated synthetic polymers that present bioactive ligands and respond to cell-secreted signals to enable proteolytic remodeling. These materials have already found application in differentiating stem cells into neurons, repairing bone and inducing angiogenesis. Although modern synthetic biomaterials represent oversimplified mimics of natural ECMs lacking the essential natural temporal and spatial complexity, a growing symbiosis of materials engineering and cell biology may ultimately result in synthetic materials that contain the necessary signals to recapitulate developmental processes in tissue- and organ-specific differentiation and morphogenesis.

NATURE BIOTECHNOLOGY VOLUME 23 NUMBER 1 JANUARY 2005 47



Fabricating Biomaterials by 3D Printing

- Generate complex-structure biomaterials
- Some methods can include cells



Review

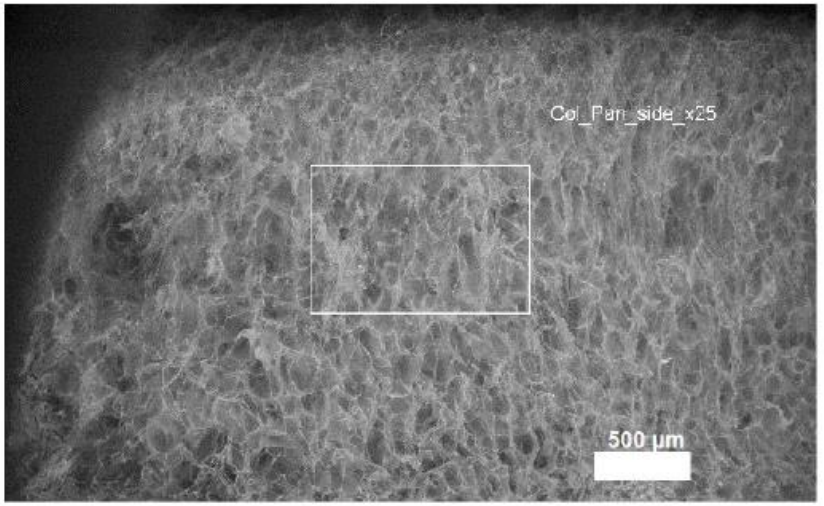
Direct-write bioprinting three-dimensional biohybrid systems for future regenerative therapies

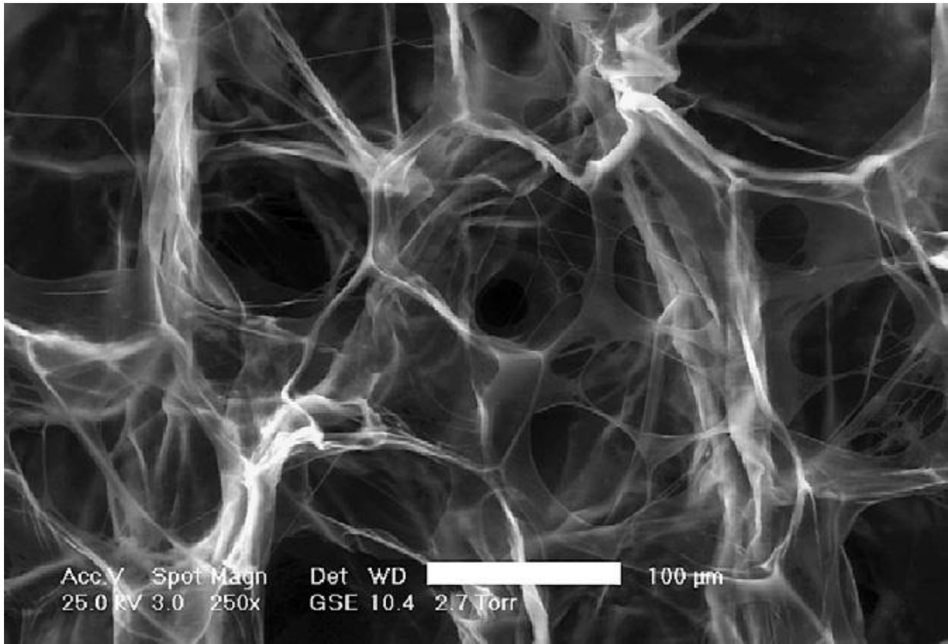
Carlos C. Chang, Eugene D. Boland, Stuart K. Williams, James B. Hoying
Cardiovascular Innovation Institute, 302 E Muhammad Ali Blvd, Louisville, Kentucky 40202

Porous Collagen Scaffolds

Porous Collagen Scaffolds

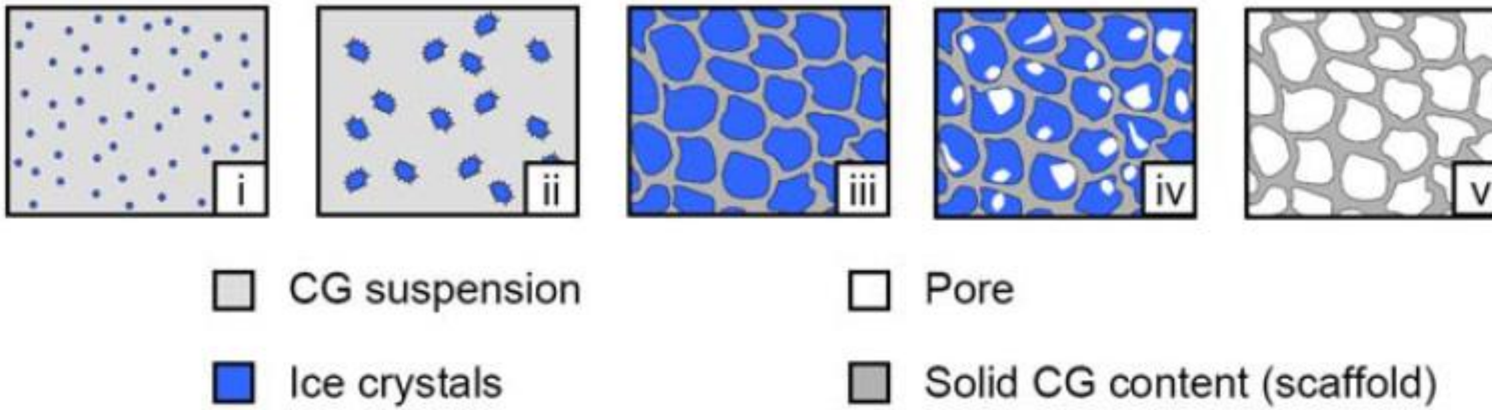
- Aka. "artificial skin"
- Key properties
  - Type I microfibrillar collagen
  - 0.5 - 5% solid fraction
  - Aprox. 100 µm pore diameter
  - Aprox 3 weeks *in vivo* half life

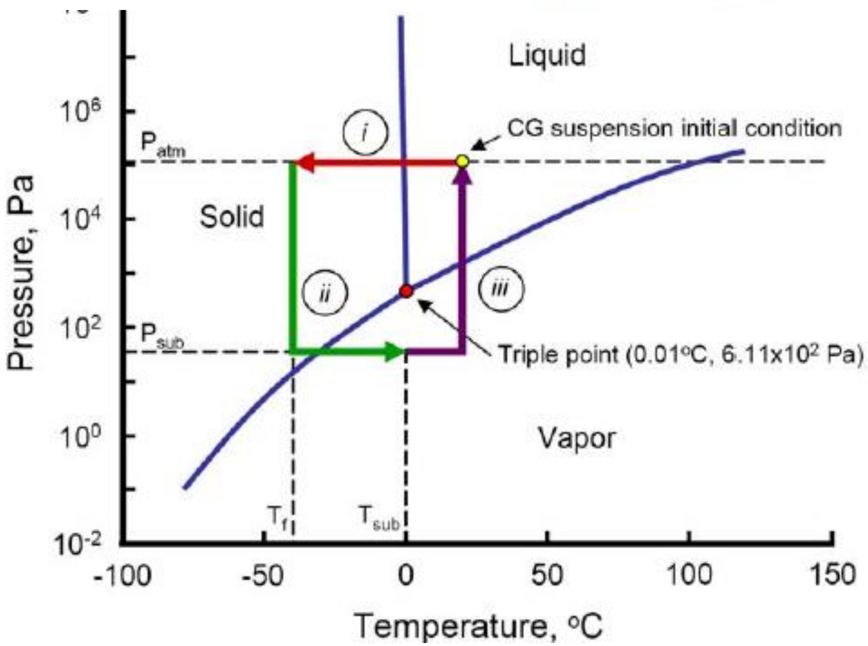


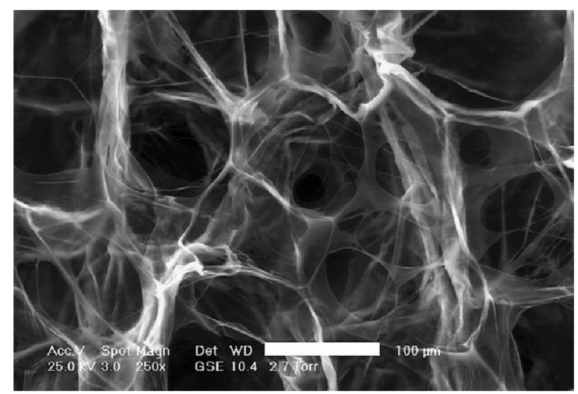


Porous Collagen Scaffold Fabrication

- Freeze-drying







Images by Harley 2012

Porous Collagen Scaffold Libraries

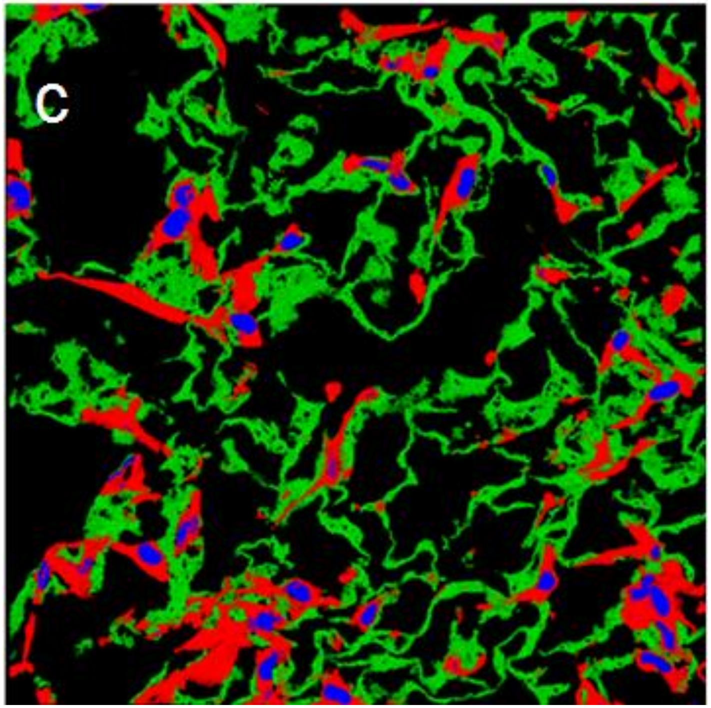
- A series of scaffolds identical in all aspects apart from a single feature
  - Pore diameter
  - Cross-linking
    - *in vivo* degradation half life
  - Chemical composition

- Optimize material parameters
  - Try to identify how biomaterials affect wound healing

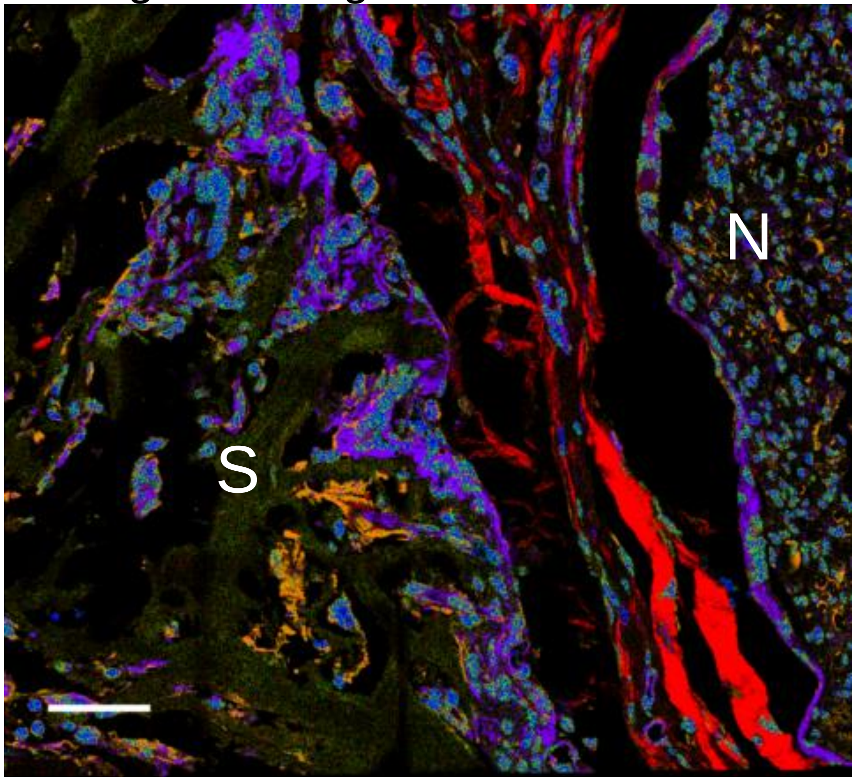
Cell-Porous Collagen Scaffold Interactions

- Binding of cells to biomaterial affect cell phenotypes
  - Cells behave differently upon binding to different materials
  - Sense different chemical clues, stiffness, topology

Fibroblasts (red, blue) binding to a collagen scaffold in vitro



Cells interacting with the scaffold (S) during nerve regeneration

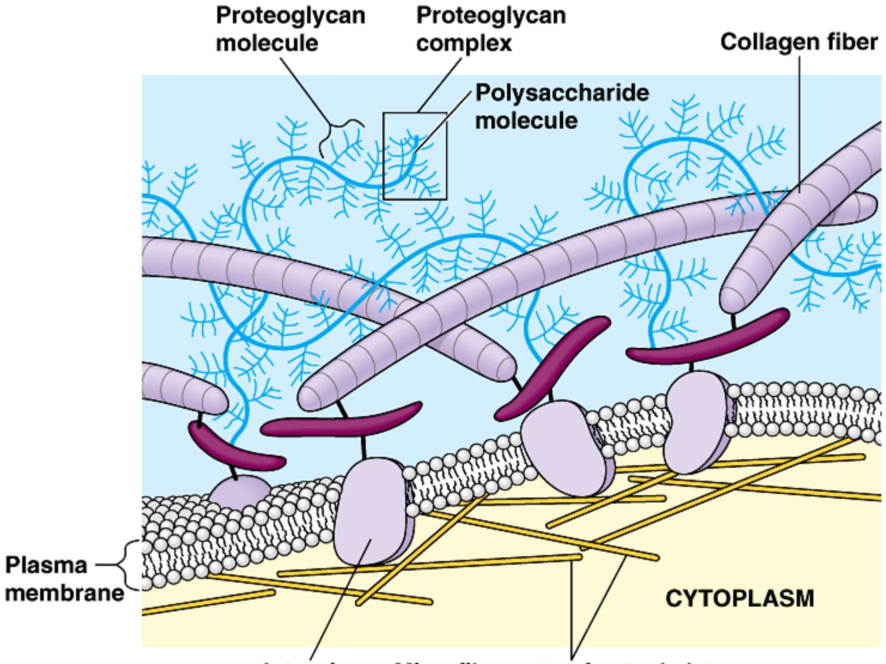


The Matrix

What is the Matrix?

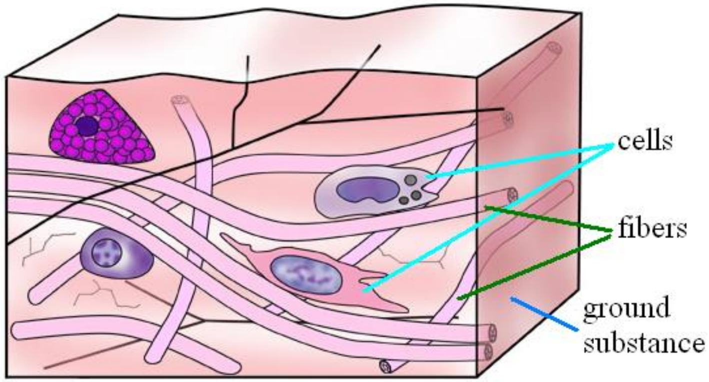
© warner bros

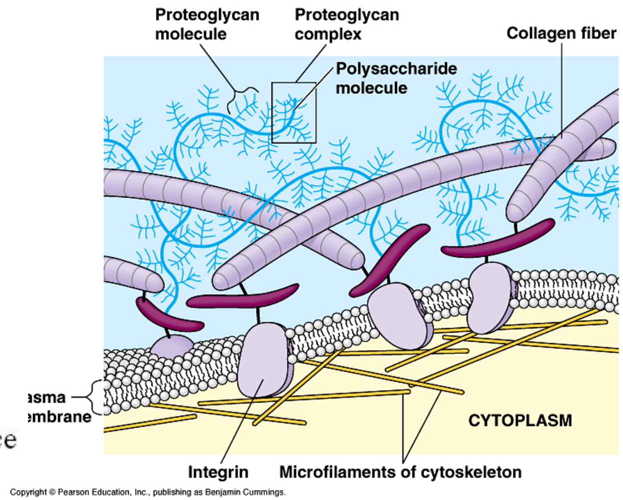
- In biology, “matrix” refers to the insoluble microenvironment of cells



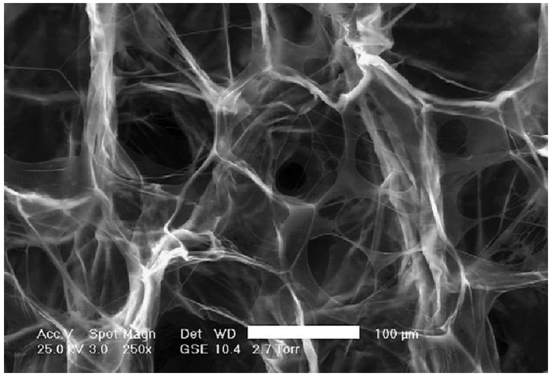
Matrix Types

- Tissue extracellular matrix (ECM)

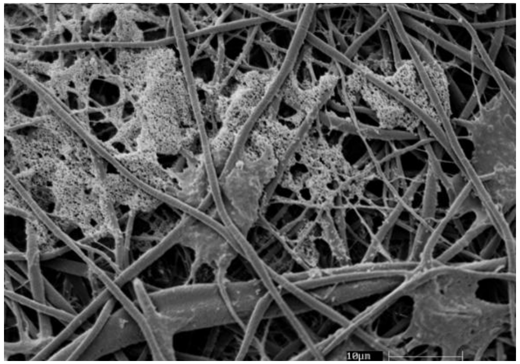




- Biomaterials



Porous collagen scaffold (Pek et al. 2004)



Osteoblasts in PLA scafold (© J. Mendenhall)

Cell-Matrix Interactions

- Cell: a system regulated by the matrix

Insoluble regulators (matrix)

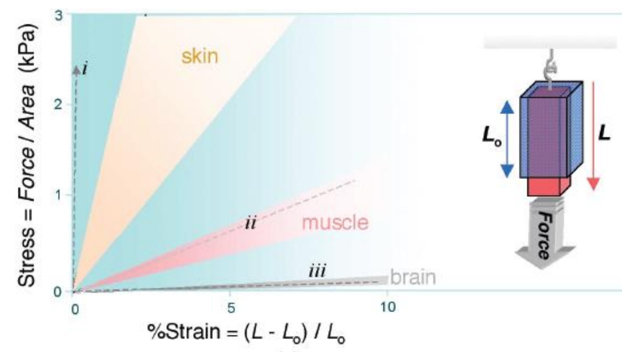
Soluble regulators (cytokines, growth factors, hormones)

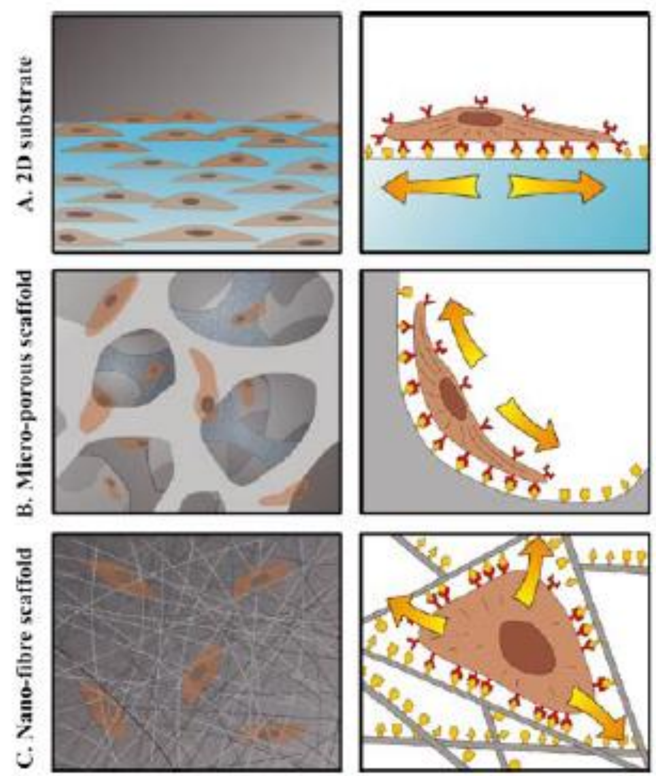
- Protein expression
- Protein modification
- Metabolism
- Force application

- Matrix regulates cells:
  - Physiology
  - Development
  - Wound healing
  - Cancer biology

Matrix Properties that Affect Cells

- Stiffness
  - Matrix deformation per cell force
- Chemistry
  - Ligands: chemical entities where adhesion receptors bind
- Topology
  - Spatial distribution of stiffness & ligands around the cell

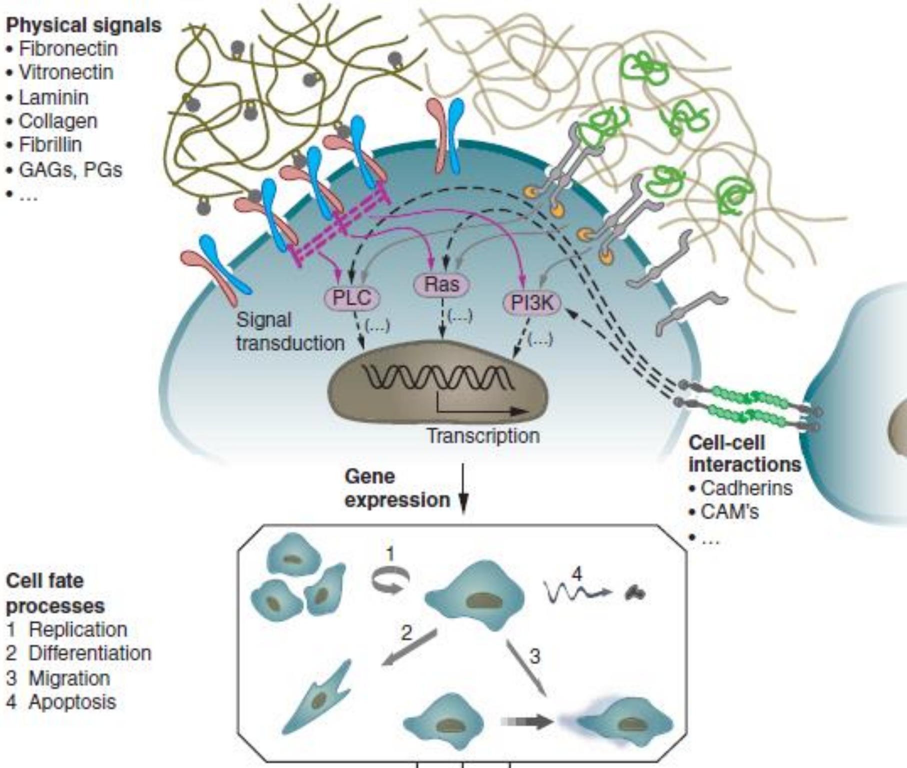




(Jell et. al. 2010)

Cell Modulation by the Matrix

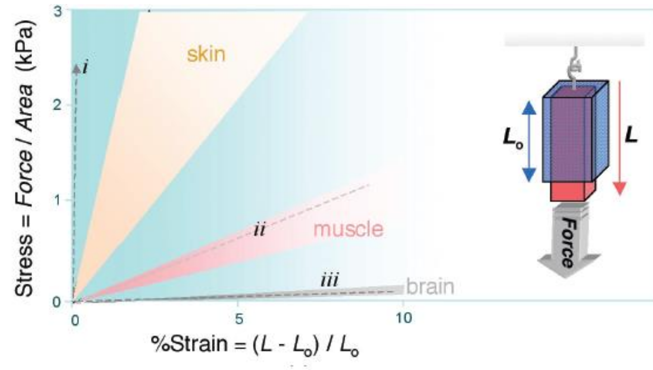
- Cells adhere to the matrix (ECM, biomaterials) using their adhesion receptors (AR)
  - Induces downstream signaling
  - Different signaling due to stiffness, composition, topology



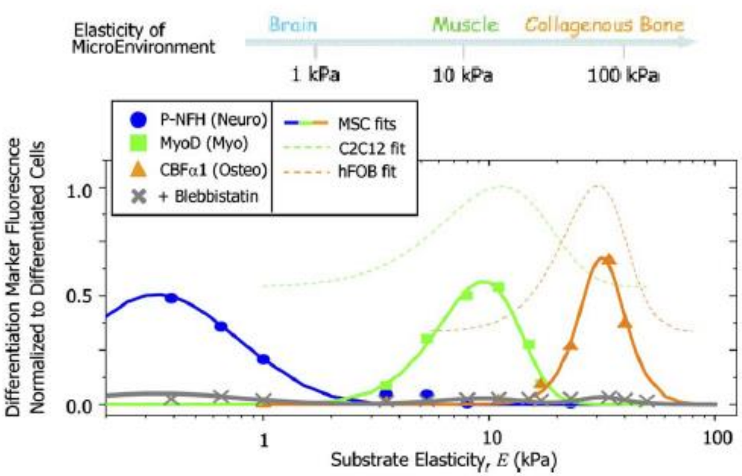
Case 1: Cell-Matrix interactions Control Stem Cell Differentiation

- The young modulus (E) of different tissues differs by orders of magnitude

- Messenchymal stem cell (MSC) differentiation *in vitro* depends on the stiffness of the cell culture substrate



Disher et al., *science, 2005*

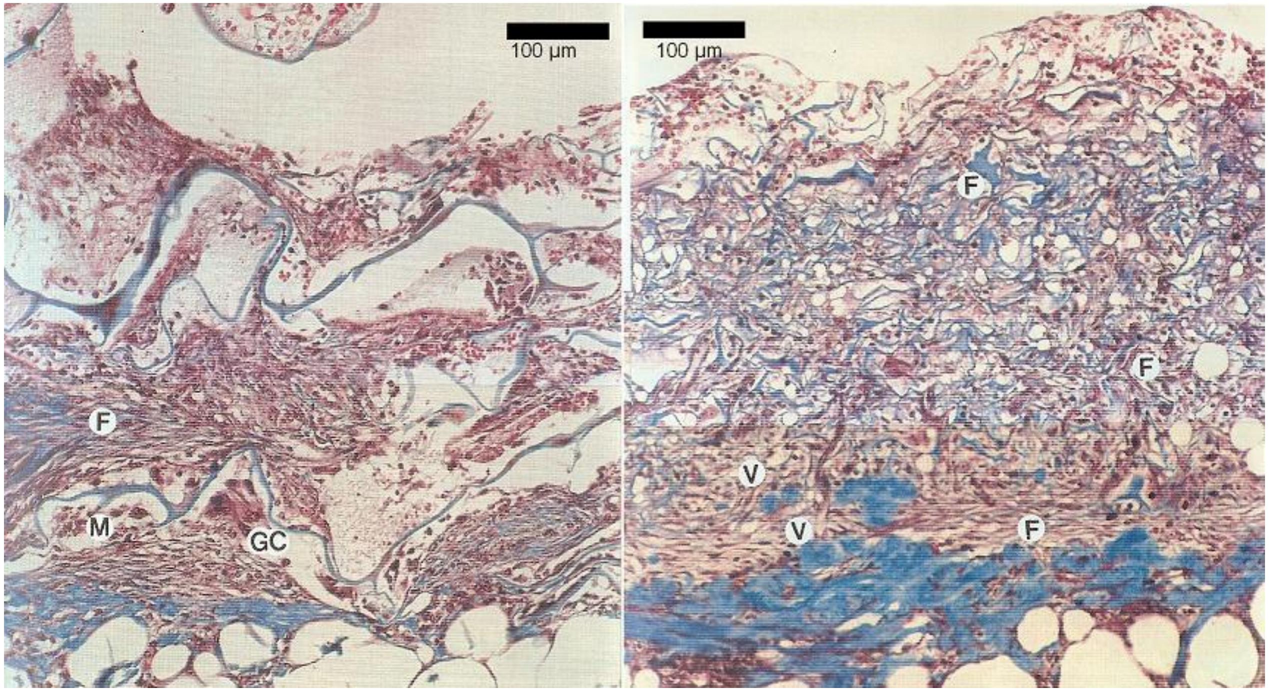

Matrix Elasticity Directs Stem Cell Lineage Specification

Adam J. Engler,[1,2] Shamik Sen,[1,2] H. Lee Sweeney,[1] and Dennis E. Discher[1,2,3,4,*]

Cell 126, 677–689, August 25, 2006 ©2006 Elsevier Inc. 677

Case 2: Biomaterial-induced regeneration

- The ability of a collagen scaffold to induce skin regeneration depends strongly on its properties
  - See next presentation



Skin grafts of different pore size regulate wound contraction in different ways (Troxel, 1993)

Key Applications of Biomaterials

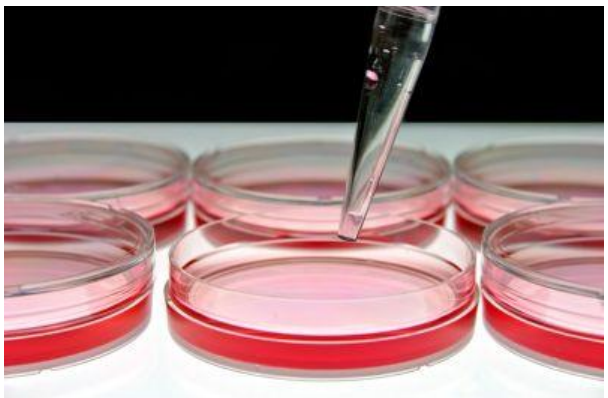
Key Applications of “Soft Biomaterials”

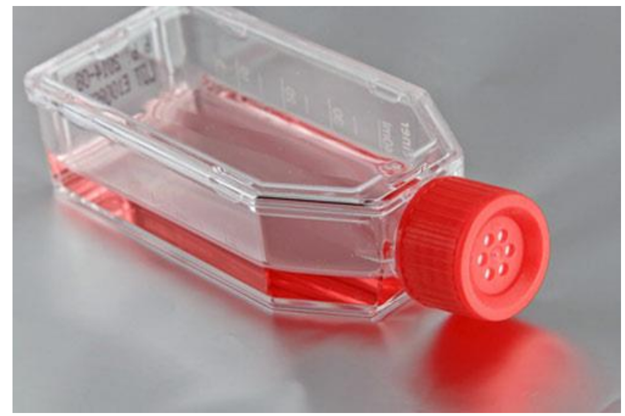
- ECM Analogs
  - Utilize biomaterials as models of tissues
  - Culture and study cells inside biomaterials

- Regenerative Medicine
  - See next presentation

Current State of Cell-based Studies

- The vast majority of cell studies take place in cells cultured in plastic flasks



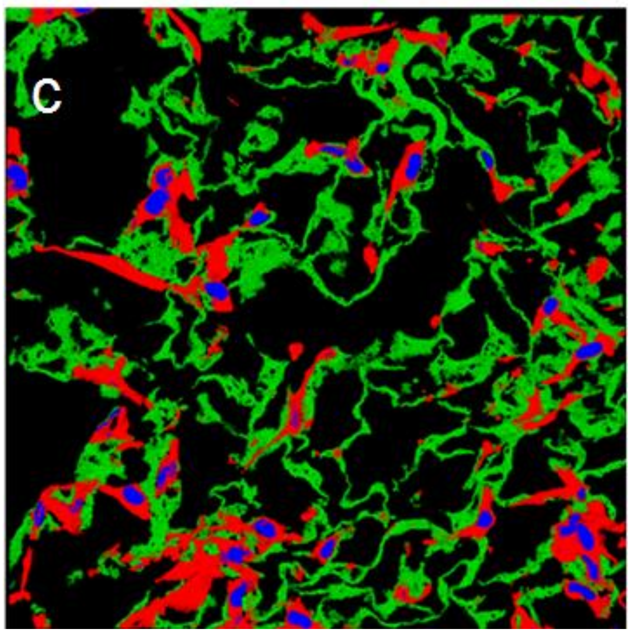


Cell culture in petri dish or flask (biotechniques.com, gegengnews.com)

  - Cells interact with a flat plastic surface
  - Artificial environment… probably affects cells
  - Need better models

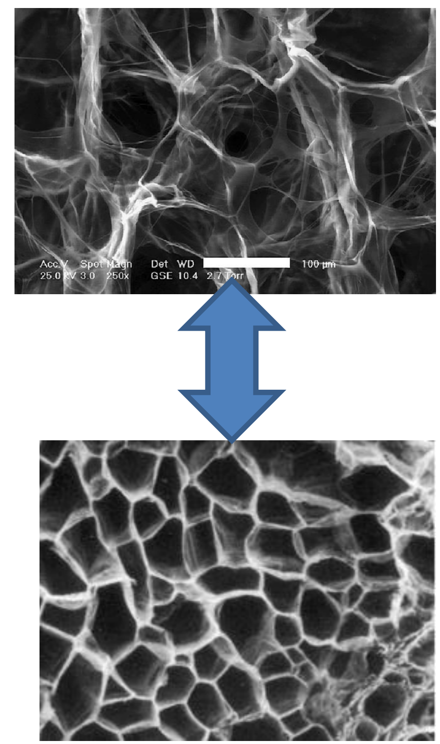
Biomaterials as ECM Analogs

- Seed and study cells inside a biomaterial
  - Biomaterial models as ECM
  - More physiologically relevant
  - Alter biomaterials → disease/tissue models



Cells (red) cultured inside a scaffold (green)
Tzeranis, 2013

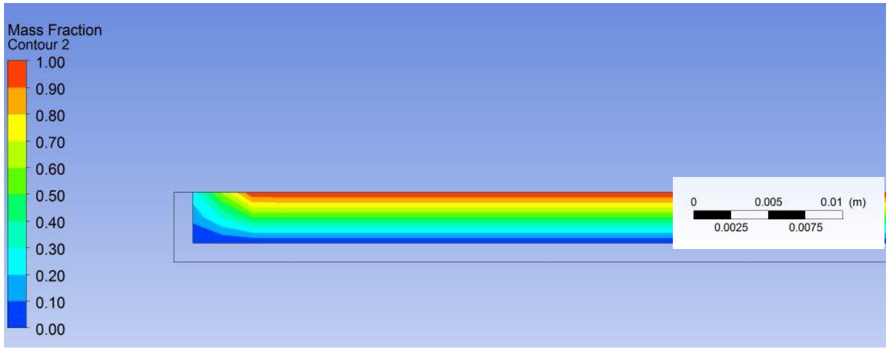
scaffold



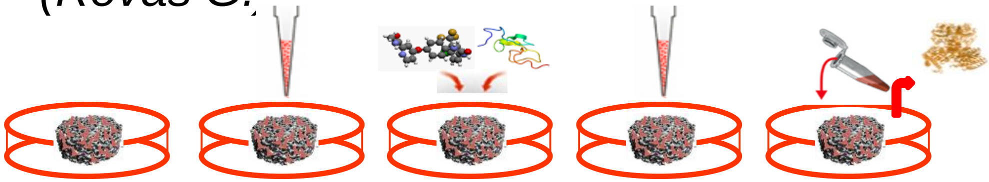
ECM

Biomaterials as ECM Analogs

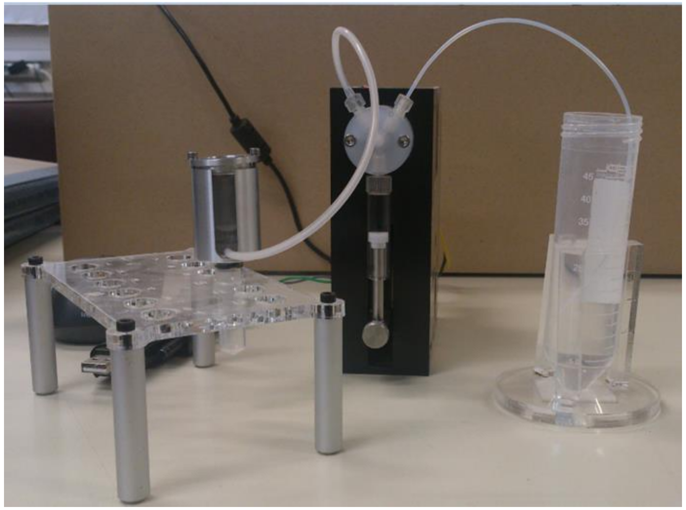
- Current research @ NTUA, IMBB-FORTH
  - Scaffold fabrication
    - Thermal modeling
    - Composition
  - Protocol optimization
    - Fibroblasts
    - Chondrocytes
    - Neural Stem cells
  - Automation
    - Need to perform 100s of experiments



Computational modeling of water freezing (Rovas G.)



Steps for conducting ELISA in scaffolds (Preza I.)

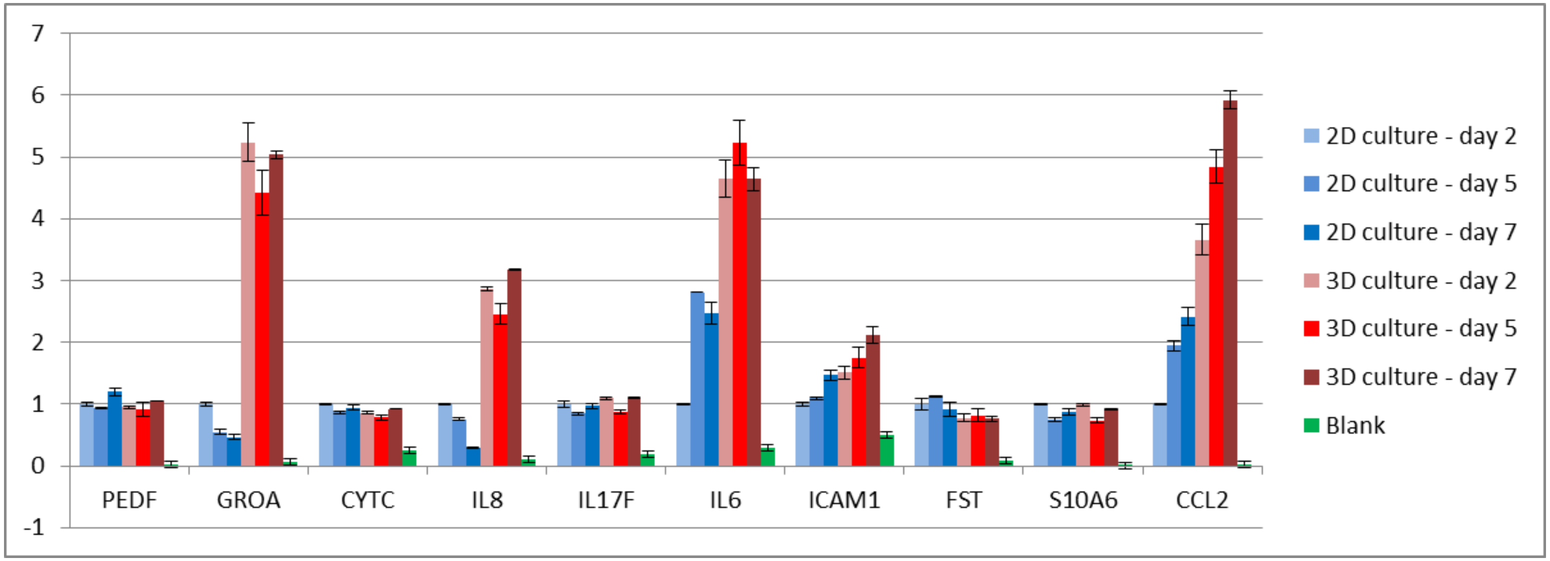


(Preza I.)

Biomaterials as ECM Analogs

- Applications:
  - Drug discovery
    - Drug toxicity
  - Disease modeling
    - ALS
  - Basic science

Comparison of cytokine secretion by fibroblasts cultured in plastic flasks (2D) or collagen scaffolds (3D) – (Marina Ioannou)



Summary

- 2 biomaterials families:
  - metal implants, soft biomaterials
- Key features of soft biomaterials: chem. composition, structure, stiffness, degradation rate
- Types of soft biomaterials: scaffolds, gels
- Porous collagen scaffolds
  - Fabricated by freeze-drying
  - Utilized in regenerative medicine
- Soft biomaterials
  - Affect cell behavior via adhesion receptors
  - ECM analogs → utilized in advanced 3D culture